Remarks

Claims 1 and 6 are hereby amended. Claims 2, 3, 5 and 7 are hereby cancelled. Claims 9 to 26 have been previously withdrawn. Claims 1, 4, 6 and 8 are therefore pending in the application. No new matter has been added by way of the present amendments.

Claim 1 as amended currently reads:

> *A method for stimulating or activating at least one of differentiation, proliferation or egress of at least one immune cell type in a human patient having neutropenia, the method comprising administering to said patient a therapeutically effective dose of at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers.*

It is submitted that claim 1 as amended is fully supported by the specification as filed. More particularly, the term "egress" is supported by page 3, lines 8-10:

> "A further aim of the present invention is to provide a method for stimulating release of immune cells from bone marrow ... "

and page 7, lines 18-20:

> "Injection of S100A8 (and all other MRPs) in the air pouch led to the migration of more neutrophils than were contained in the blood, suggesting that it induced the release of neutrophils from the bone marrow."

In addition , Figure 3 contains graphs clearly showing PMN (neutrophils) increase in blood along with a PMN decrease in bone marrow.

Claim 6 as amended currently reads:

> *The method of claim 1, wherein said human patient is a patient having neutropenia associated with at least one of: cancer, anti-cancer chemotherapeutic treatment or bone-marrow transplant.*

It is submitted that claim 6 as amended is fully supported by the specification as filed. More particularly the terms "bone marrow transplant" can be clearly inferred at page 9, line 2:

"... MRP can be preferably used for immuno-suppressed patients... "

as well as in the abstract:

"...for reducing the risks of microbial infections in patients immuno-supressed."

No new matter has been added by the present amendments.

Objections to the specification

The objections to the specification have been addressed in the amendments to the specification enclosed herewith. Applicant wishes to thank the Examiner for pointing those out.

Claim rejections

The Examiner has rejected claims 1-8 under §112 first paragraph because of the expression "S100 proteins and derivatives thereof" for lack of written description presumably because the broad genus (i.e. all S100 proteins and derivatives) has not been fully described in the specification. Strictly in order to advance prosecution, Applicant has amended claim 1 to read: "*...at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers,..*". This amendment is based on support found in the specification as filed at page 7 ,lines 24-25. This amendment is believed to render the rejection moot and the Examiner is respectfully requested to withdraw this rejection.

The Examiner further rejects claims 1-8 under §112 first paragraph because the claims presumably do not provide enablement for "1) inhibiting or inactivating the immune cells; 2)using other S100 proteins or derivatives; or 3) administering to any patient." Claim 1 has now been amended to reflect what the examiner has stated in the office action (page 7) to be enabled. Withdrawal of this rejection is therefore respectfully requested.

The Examiner further rejects claim 1-5 and 8 under §102 because presumably these claims are anticipated by Devery *et al.* (J. Immunol. 1994) because this reference discloses the administration of CP-10 and/or MRP-8 into mouse footpad.. Claim 1 has been amended to define the patient as " a human patient". Amended claim 1 is therefore not anticipated by this reference and the rejection is rendered moot. Withdrawal of this rejection is therefore respectfully requested.

The examiner further rejects claims 1-5 and 8 as presumably anticipated by Halle *et al.* (US 2003/0003482) because this reference teaches the use of MRP8 and/or MRP14 for treating and/or preventing skin diseases and wounds in patients. Claim 1 as amended recites "a treatment for neutropenia", which is clearly distinguishable from skin wounds and diabetic ulcers and therefore patentably distinct. Withdrawal of this rejection is therefore respectfully requested.

The Examiner rejects claim 6 and 7 as being obvious in view of Devery *et al.* (supra) in view of Fidler (Cancer Res. 1985) because these references when combined presumably renders obvious "the activation of macrophages and treatment of metastasis in a cancer patient." With respect, claim 1 now claims: "*A method for stimulating or activating at least one of differentiation, proliferation or egress of at least one immune cell type in a human patient having neutropenia, the method comprising administering to said patient a therapeutically effective dose of at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers*" whereas amended claim 6 now claims that: "*... said human patient is a patient having neutropenia associated with at least one of: cancer, anti-cancer chemotherapeutic treatment or bone-marrow transplant.*"

Devery *et al.* teach accumulation and infiltration of neutrophils and macrophages of normal mouse having a normal immune system. This is not the case here. Applicant is teaching about a patient having a diminished immune system whether it is caused by the cancer itself, cancer chemotherapy or even bone marrow transplant immunosuppressive therapy. The invention here resides in the unsuspected and unexpected fact that S100 proteins when injected *in vivo* in a human patient produce a stimulation in the bone marrow that **induces maturation of precursor cells into mature and functional immune cells, proliferation of these mature immune cells as well as egress (i.e. migration from the bone marrow into the circulation)** thus helping the patient recover a "normal" immune system. This is being accomplished irrespective of any anti-

cancer treatment and is not done in order to get rid of cancer cells but rather in order to address the causes and symptoms of neutropenia (i.e. a decrease in number and functionality of immune cells in the bone marrow). Support for this contention is found in the application as filed and particularly in Figure 3

Devery et al,. stresses that their results report to chemotaxis and neutrophil infiltration:

> *The murine S100 chemotactic protein of m.w. 10,000 termed (CP-10), has* ***potent chemotactic activity*** *for murine and human myeloid cells. We examined the ability of a synthetic CP-10 hinge region peptide CP-10 $_{(42\text{-}53)}$ and rCP-10 to act as* ***chemotactic agents*** *and induce expression of the adhesion molecule Mac-1 (CD 11b/CD 18) in vivo. Maximal neutrophil (PMN) accumulation occurred between2 to 8 h after mouse footpad injection of rCP-10 (10^{-7} M) or CP-10 peptide (10^{-6} M). The* ***infiltrating PMN*** *expressed high levels of Mac-1, and low levels of the murine L-selectin Mel-14. Injection of CP-10 peptide i.p. also* ***induced infiltration of PMNs*** *that expressed high levels of Mac-1. Cell suspensions obtained after i.p. injection of CP-10 peptide could be significantly inhibited from adhering to fibrinogen-coated plates when incubated with anti-Mac-1 antibody. The* ***chemotactic activity*** *of CP-10 peptide toward murine inflammatory PMN in vitro was also inhibited by anti-Mac-1 antibody. Neither or granular enzyme release. The localization of CP-10 may contribute to the generation of a* ***chemotactic gradient.***

Egress is conceptually very different from chemotaxis (see ref. Roskinski *et al. Annals of Biomed. Eng.* 2004 Vol 32, No. 8 pp1108-1119 *Quantitative dynamic of in vivo bone marrow neutrophil production and egress in response to injury and infection.)*:

> *Our conceptual model of BM neutrophil production is shown in Fig. 1, and consists of a* ***self-renewing neutrophil progenitor pool (N_P) and a nonproliferative neutrophil maturation pool (N_T). The progenitor pool contains a continuum of developmental stages, from the most primitive stem cells through to proliferating myelocytes, with an overall proliferation rate defined as $^{V}1$.*** *Ideally, the* ***proliferating pool immediately preceding the mature neutrophil pool*** *would be studied, but a clear unambiguous phenotype is not available. Therefore, we consider* ***all precursor cells as a single population of progenitor cells that are eventually destined to become neutrophils. Cells leave the progenitor pool at a rate $^{V}2$ to enter the maturation pool containing neutrophils, which no longer proliferate. The maturation pool can be imagines as a holding tank for cells that migrate into the peripheral blood at a rate $^{V}3$.*** *In order to estimate these rates, we use the DNA label BrdU, and assume that all proliferating cells in the S-phase become labeled instantaneously. Assuming no proliferation within eh mature neutrophil pool, BreU-labeled cells* ***enter this pool solely via differentiation of progenitors.*** *We assume an age-independent probability for neutrohil egress ($^{V}3$) where* ***each cell in that pool has the same probability of entering the circulation.***

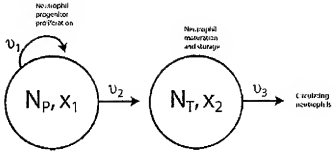


FIGURE 1. Conceptual model for neutrophil production in the bone marrow. See text for explanations.

In other words, chemotaxis implies infiltration and accumulation of immune cells at the site of infection (i.e. acute inflammatory response) whereas egress implies the migration of immune cells from the bone marrow into the peripheral circulation (i.e. blood or lymph).

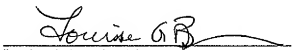
The Examiner stipulates that the combined teachings of Devery *et al.* and Fidler provide a reasonable expectation of successfully treating metastatic cancer. With respect, claim 6 is not directed to a method for treating metastatic cancer but to a method for inducing immune cells maturation, proliferation and egress, irrespective of whether the patient has cancer or not. A person skilled in the art, trying to accomplish the invention as currently claimed would have found no motivation in Devery *et al.* since the mouse used for experimentation had a normal and functional immune system. Successful transposition from a normal mouse to a neutropenic human patient is neither straightforward, nor expected without using hindsight. The Examiner is therefore respectfully requested to withdraw this rejection for obviousness under Devery *et al.* in view of Fidler.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the examiner's rejections is respectfully requested and allowance of claims 1, 4, 6 and 8 at an early date is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

No fee is believed to be required by the present response. However, should this be an error, authorization is hereby given to charge deposit account 19-5113 for any underpayment or to credit any overpayment.

Respectfully submitted,



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